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OPHTHALMIC DRUGS SUBCOMMITTEE OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

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Kevin R. Frost

C O N T E N T S

P R O C E E D I N G S

CHAIRMAN WILSON: I'd like to welcome everybody, first of all, to this meeting. This is the Ophthalmic Drugs Subcommittee of the Dermatologic and Ophthalmic Drugs Advisory Committee.

I'd like to start off, first of all, by having the members introduce themselves. I'd like to remind everybody to speak into the microphones because all of this is being taped, and maybe if we can start off to the left and work our way around?

MS. COHEN: I'm Susan Cohen, and I'm the consumer member.

DR. KILPATRICK: Jim Kilpatrick, Medical College of Virginia.

DR. FONG: Donald Fong, Kaiser Permanente Medical Center.

DR. CHEW: Emily Chew from the National Eye Institute, National Institutes of Health.

CHAIRMAN WILSON: I'm M. Roy Wilson from Drew University.

MS. McGOODWIN: I'm Ermona McGoodwin, FDA.

DR. MATHEWS: I'm Chris Mathews, University of California-San Diego.

DR. BIRNKRANT: Debra Birnkrant, Deputy Director, Division of Antiviral Drug Products.

DR. CHAMBERS: Wiley Chambers, Deputy Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

DR. DeLAP: Bob DeLap, Office of Drug Evaluation V, FDA.

DR. LUDWIG: Elizabeth Ludwig, Medical Officer, FDA.

CHAIRMAN WILSON: Ermona McGoodwin will now read the conflict of interest statement.

MS. McGOODWIN: Thank you, Dr. Wilson.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and the information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to FDA's invited guests, there is a

reported interest which we believe should be made public to allow the participants to objectively evaluate his comments. Mr. Kevin Frost, who will be coming, would like to disclose for the record that he has served on the Data and Safety Monitoring Board for several of ISIS Pharmaceutical's clinical studies related to Vitravene.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

xx CHAIRMAN WILSON: We'll move on to the open public hearing. There are two requests to speak. The first is Reena Lawande. Is she here?

MS. LAWANDE: Thank you. Good morning. My name is Reena Lawande, and I'm from Project Inform in San Francisco. I'm speaking today presenting comments on behalf of Ben Chang, who is the Associate Director of the Information and Advocacy Department at Project Inform, who unfortunately couldn't make it here today.

Project Inform is a national HIV treatment information and advocacy organization that serves over 100,000 people with HIV and their caregivers every year. In the interest of full disclosure, I just want to note that Project Inform has never received any funding or grants from

either ISIS Pharmaceuticals or Ciba Vision, and neither has paid for our travel expenses to attend this meeting.

As an organization which has been in the front lines in the fight against AIDS since 1985, we have been encouraged by the decrease in opportunistic infections and deaths with the advent of highly active antiretroviral therapies. However, we also serve a large number of constituents who have never benefited from the protease inhibitors or who have already failed or who are intolerant to these therapies. Most of these people are already at an advanced stage of HIV disease and, as a result, have had or are at risk of developing CMV disease or other opportunistic infections.

We believe that the studies on fomivirsen have shown good activity against CMV retinitis and that the drug will be a very useful addition to the armamentarium of therapies against this disease.

While Project Inform has noted the small size of the packet submission, we do believe that the data presented today certainly do demonstrate that the drug is safe and effective against CMV retinitis.

In light of the small numbers of people with CMV retinitis today and the difficulties in enrolling participants in these studies, we feel that the sponsor has attempted to answer all of the critical questions on the

safety of the drug and how best to use this therapy.

Therefore, we believe that fomivirsen, with its different mechanism of action and its activity against CMV strains that appear to be resistant to current therapies, such as Ganciclovir, Foscarnet, and Cidofovir, should be made a therapeutic option for people with CMV retinitis.

We also feel that the reduction in the number of people with opportunistic infections and the difficulty in enrolling participants for studies such as these may result in the future in a decreased effort from industry to develop new therapies for these diseases, and we would encourage the FDA to offer guidance on how to develop new therapies for these indications in the future. With few new therapies in development for treating HIV, we worry that the incidence of opportunistic infections will begin to increase, and we will then have to begin to play almost catch-up with the development of new therapies for these conditions.

It is important to remember that there still remains a sizable number of people who need new therapeutic options to treat CMV retinitis, and Project Inform hopes that the committee will support approval of fomivirsen for the treatment of this disease.

Thank you for the opportunity to speak this morning.

CHAIRMAN WILSON: The next requested speaker is

Christopher Smith. Is Christopher Smith here?

MR. SMITH: My name is Christopher Smith. I'd like to start out by saying that just my travel was paid for by ISIS to come here. I am not receiving monetary incentives. The incentive that I am receiving and have received for the past two and a half years is the fact that I can stand here today and see every one of you.

Six years ago, I was diagnosed with HIV and full-blown AIDS here in D.C. and had a very low T-cell count to start with. After two years, I was going to the eye doctor's about once every three months with the fear that I would have CMV retinitis.

After two bouts of pneumonia, quitting my full-time job, and by liquidating a life insurance policy, I was trying to live out the last days of my life traveling and doing the things that I wanted to do. When I got back New Year's Day in 1996 and I knew something was wrong, I went to the eye doctor and was diagnosed with CMV retinitis.

The visions I had about the disease were from literature and also the movies. Paul Monette (ph) did a wonderful job portraying his lover's fight with his eyesight in "Borrowed Time." The last scenes of "Philadelphia" show Tom Hanks walking around with an IV pole in his arm for up to four hours a day. And "Long Time Companion" was another one that struck fear in me, just the fact of losing so much

so far and having the threat of losing my sight.

Luckily, I was hooked up with Dr. Deborah Goldstein at the University of Illinois, and she presented the treatment options to me: the IV Foscarnet and IV Ganciclovir. I had plenty of friends who had the toxic side effects to both their bone marrow and their kidneys, were forced to be removed from the drugs, and subsequently lost their sight as soon as they were removed from the drugs. These options and my travel plans didn't fit together. The Ganciclovir implant was not available, and the option that I chose was ISIS 20-922 and enrolled myself in the CS2 study.

That was two and a half years ago. The study was supposed to last for 18 weeks. I am now on week 130. When I go back to Chicago next Tuesday, I will have my 65th injection. My eyesight has not gotten any worse in the eye that's injected, and my lesion is totally quiescent.

In the two and a half years that I was doing this, I would get an injection on Tuesday. I would board a plane Tuesday night and decide where I wanted to go for two weeks, and then come back the next Tuesday--a week from Tuesday to get the next injection.

I tried, and succeeded, to shrink down the amount of time that this took in my life to about four hours a day every two weeks. I'm one of the patients who has failed HAART and am currently not taking any antiretrovirals. My

T-cells have been at zero for two and a half years. My viral load has been over 750,000 for that same time also. Yet my eye is fine.

I have been able to go to Amsterdam, see the Keukenhof Gardens, see the Vermeer collection, travel to Geneva, Paris. There's lots of friends across the United States, and without this drug and without being in this study, I don't think that that could have happened.

So I do have a vested interest in this passing, so that I don't have to go on one of the other therapies.

I guess that's it--oh, one other thing I should say is that one of the reasons why I am here is because I'm a teacher by training. I am a research chemist also. And I left the laboratory life. I left the research teaching, and ironically find myself as a subject in a research project instead of the person who's conducting it. And I still feel that I am contributing, which is helpful to any AIDS patient's psychological well-being.

Thank you very much.

CHAIRMAN WILSON: Thank you.

We've had two latecomers coming in, and I would like to ask them to please introduce themselves for the record.

MR. FROST: I'm Kevin Frost. I'm the Director of Clinical Research and Information at the American Foundation

for AIDS Research, AMFAR, in New York.

DR. HANNUSH: I'm Sadeer Hannush, Associate Surgeon, Cornea Service, Wills Eye Hospital, Philadelphia, Pennsylvania.

CHAIRMAN WILSON: Is there anybody else that would like to speak in the open forum?

[No response.]

CHAIRMAN WILSON: If not, we'll move on to the introductory remarks of Dr. Chambers.

xx DR. CHAMBERS: Thank you, Dr. Wilson. I would just like to welcome everyone to this meeting, and thank you for your participation.

The drug product that we are going to talk about today is the result of a number of investigations over a relatively--well, over a number of years. Several interactions have occurred between the sponsor of this application and FDA. There have been discussions about how many patients that would be needed, what should be shown, and the realities of the number of patients that have CMV retinitis in the United States right that are available for study.

As is evident from my review and I'll discuss later on, the number of patients that were studied is small, and there were discussions with the FDA about whether this package was sufficient for submission. The agency a number

of months ago recommended to the sponsor that they not submit the application because the numbers were small.

In the intervening time, with the inability to recruit additional patients, there was a clear realization that additional progress was not being made. The agency therefore accepted the NDA application at the time that it came in. That does not mean it would not have been our preference to have more patients. But that's the reality, and you see the package that we saw.

The agency at this point has not made a decision about whether this is approvable or not approvable. As you can tell from my review, there are various issues that still remain, but we are seeking additional input. As I say, I cannot stress enough the decision has not been made. We do not read anything into my review one way or the other. We are looking for additional input about whether this would be a useful therapy and, if so, in what context the therapy would be useful.

I welcome any comments, any questions, at any point as we go along. Again, I thank you very much.

CHAIRMAN WILSON: We'll move on to the scientific session. The first presenter for ISIS Pharmaceuticals is Lisa Grillone.

DR. GRILLONE: Good morning. My name is Lisa Grillone. I'm the project leader for fomivirsen. I'd like

to take this opportunity to thank the members of the panel and the members of the Food and Drug Administration for allowing ISIS Pharmaceuticals the opportunity to present to you this morning the data, the safety and efficacy data, for fomivirsen for your consideration in the approval of this compound for the treatment of CMV retinitis, both for newly diagnosed disease and for previously treated disease.

The agenda this morning consists of Dr. Kisner, first of all, who is our president and chief operating officer. Dr. Kisner will provide the introduction. Dr. Chandler, who is an ISIS consultant and a practicing ophthalmologist, will present the clinical data for safety and efficacy on fomivirsen. Your questions and answers will be addressed by Drs. Kisner, Chandler, myself, and others from ISIS Pharmaceuticals.

At this time I'd like to invite Dr. Kisner to the podium to begin. Thank you.

DR. KISNER: Good morning. It's a pleasure for me to be here to present to you the clinical package for fomivirsen. Fomivirsen is the first antisense oligonucleotide that's been presented as a new chemical entity for approval to any regulatory agency, and we will go through a small amount of discussion of antisense pharmacology at the beginning of my remarks.

After that, I'll provide a general description for

you of fomivirsen. I'll go on to attempt to put this package and this discussion into the perspective of what's going on in HIV and in CMV disease today. I'll spend a few minutes only on the currently available therapies, their advantages and disadvantages, and describe for you what we believe to be the residual therapeutic need in CMV retinitis. I'll go on to describe for you what I believe the fit is with regards to fomivirsen's characteristics and the therapeutic need. I'll describe briefly the clinical program that you'll be hearing from Dr. Chandler about, lay out the key questions that both we and the agency agree are critical for discussion and deliberation today, and I'll finish with an introduction of Dr. Chandler himself.

Next slide?

As I said, fomivirsen is the first antisense oligonucleotide to come before a panel like this, and it's important to go through the pharmacology just briefly.

Traditional drugs, small molecules shown here, tend to be designed to bind the proteins involved in human disease, receptors, enzymes. They bind to those proteins, modify their structure, modify their function, and hopefully have some salutary effect on the disease without too much in the way of toxicities. Antisense drugs work one step further back in the process. The process I'm talking about is the business of producing the proteins that are involved

as mediators or causative agents in human disease. Antisense molecules bind at the level of messenger RNA, which is transcribed from the information stored in double-stranded DNA, and they bind directly to the messenger RNA. And by a series of, a variety of mechanisms, actually, after the binding, they prevent the production of the protein that's encoded that is involved in the human disease process itself.

Antisense drugs bind to messenger RNA using a binding motif that is identical to the one that holds together the double-stranded helix of DNA, Watson-Crick base pairing. So antisense compounds are an entirely new chemical class of drugs, that is, antisense oligonucleotides. They use an entirely new binding motif to bind to a target, that is, Watson-Crick base pairing, and they use an entirely new molecular target for drug therapy, messenger RNA. In the case of fomivirsen, the DNA and RNA in question are viral DNA and RNA.

Next, slide, please?

Fomivirsen itself is an oligonucleotide of 21 nucleotides in length, a 21-mer oligonucleotide. It is designed to be complementary to the messenger RNA sequence for the immediate early gene product of human CMV. This product is a key regulator of gene expression in CMV and absolutely critical for replication of the virus.

Inhibition of the production of that gene product is therefore an antiviral strategy.

The molecule itself is a 21-mer phosphorothioate oligonucleotide. That means that at every phosphorous on the backbone, there is a substitution of sulfur. This enables the molecule to be resistant to nuclease degradation, provides stability that allows these oligonucleotides to function as drugs in tissues.

Next slide.

Fomivirsen is a potent antiviral against human cytomegalovirus with an EC50 of 0.03 micromolar in human retinal pigment epithelial cells and approximately 0.34 micromolar in human fibroblasts. It is therefore at least 10- to 30- or 40-fold more potent than Ganciclovir on a molar basis, depending upon the experiments one looks at. Most importantly, fomivirsen retains full potency against strains of human cytomegalovirus that are resistant to the currently available DNA polymerase inhibitors. There is no cross-resistance.

Next slide.

This discussion is important to put into the context of what's happening in HIV and CMV today, and this slide contains some good news at the top and some concerns at the bottom.

The thing that we can all agree on is that the

good news is that highly active antiretroviral therapy, protease inhibit-based combination therapy, has made a dramatic difference in the shape of this epidemic. The patients are achieving durable and profound remissions of their HIV disease today, and this has resulted in a profound drop in the incidence of newly diagnosed opportunistic infections, with regards to CMV retinitis, perhaps as high as 70 to 85 percent. For certain, this has made an orphan indication a rare disease, and I can tell you it's made it extremely difficult to study this disease over the last two or three years.

The concerns are shown here. Resistance to HAART therapy has been described. It's being described in more therapy. Multi-drug resistance of protease inhibitors is being described. Patients are beginning to fail HAART therapy. Furthermore, intolerance to HAART therapy has been described with increasing frequency. Patients are having difficulty with side effects, body fat distribution problems, lipid abnormalities, diabetic complications. And the difficult-to-take regimens have resulted in poor compliance with these regimens, and that's making resistance a bigger problem, at least in most people's opinion.

On the CMV front, cross-resistance to DNA polymerase inhibitors has been described for some time, but most concern is that resistance to CMV is increasing and has

been reported to be increasing in recent years. Resistant strains are out there and represent a problem. And I think it's also true that because of the good news at the top, the level of interest in research in opportunistic infections has really fallen off in recent years, especially research having to do with new agents. The concern we have, of course, is that with a resurgence of HIV disease that may happen should HAART therapy continue to fail, CMV disease, CMV retinitis may resurge, with resistant strains of virus becoming much, much more common.

Next slide.

Currently available therapies are, one and all, DNA polymerase inhibitors. With the exception of oral Ganciclovir, they require intravenous infusion or surgery to place an implant. They have some disadvantages with regards to the systemic IV drugs. I'll describe those in just a moment. With regards to the surgically placed implant, there is a requirement for surgery--in fact, for multiple surgeries, and, again, the risk of surgery includes infection, retinal detachment, and other complications with Ganciclovir implants that you're fully aware of.

Again, every one of these drugs has been reported to be suffering from increasing levels of resistance in recent years, and cross-resistance is going to remain a problem for the future.

Next slide.

The systemic toxicities are well-known to the committee of the systemic DNA polymerase inhibitors. Bone marrow suppression occurs, renal insufficiency in a couple of the drugs, gastrointestinal side effects, catheter infections that may frequently lead to systemic infections. For many patients treated with systemic DNA polymerase inhibitors, the costs that they pay in terms of toxicity is considerably high in exchange for the level of therapeutic benefit that they achieve.

Next slide.

We believe there are residual therapeutic needs in CMV retinitis, and they're listed on this slide. We believe there's a need for drug or drugs that have a rapid onset of durable control of this disease; that have a favorable safety profile, both the systemic profile as well as a local safety profile; that offer convenient dosing, dosing that allows patients to maintain a maximal quality of life as they deal with the other complications of HIV disease; and, most importantly, for drugs that have no cross-resistance to currently available DNA polymerase inhibitors.

Next slide.

We believe that fomivirsen fits the bill for these therapeutic needs quite well. We'll demonstrate for you today that the drug has a rapid onset of disease control, as

demonstrated by decreased border opacification; that that control is durable; that it's achieved with an acceptable ocular safety profile, including a low retinal detachment rate; that it's achieved without systemic side effects; that it is achieved with intravitreal dosing at convenient intervals, well tolerated and at convenient intervals, as infrequently as once a month; and, most importantly, we'll show you that the drug is effective for the treatment of patients clinically resistant to currently available drugs, DNA polymerase inhibitors for this disease.

Next slide.

Dr. Chandler will describe for you in detail the clinical package. On the efficacy side, you'll see two studies discussed. The first is CS2. This is a classic delayed-therapy study in which the 165-microgram regimen that you'll hear about is compared in a random fashion to patients allocated to delayed therapy. These are newly diagnosed patients with peripheral CMV retinitis.

In patients with previously treated and uncontrolled retinitis, you'll see a study that compares two different schedules of fomivirsen at a 330-microgram dose, a more intensive versus a less intensive schedule of administration.

Next slide.

Other studies that will not be presented here that

are shown on this slide have been used to generate the integrated efficacy and the integrated safety information that you will hear from Dr. Chandler about. There will be a brief discussion of the results of the clinical pharmacokinetic study, CS5.

Next slide.

These are the key questions for the discussion of this package today. Is fomivirsen efficacious? Is fomivirsen safe in the dosing schedules that we're recommending use? And is the data set available to you adequate for full review and assessment of the package label claims that we've made?

Next slide.

The balance of this discussion will be presented by Dr. John Chandler. Dr. Chandler is a former professor and chairman of ophthalmology at the University of Wisconsin and University of Illinois. He was a member of the National Advisory Eye Council for NEI the years '88 to '93. He chaired the program committee responsible for the last five-year vision research plan for the National Eye Institute. He is the immediate retiring past chairman of the Board of Scientific Counselors for the National Eye Institute. Dr. Chandler has been a consultant to ISIS Pharmaceuticals since the beginning of the fomivirsen development program. He has been a member of our Data Safety Monitoring Board. He has

been intimately involved in the development of the analyses and the documents that you've seen and that were submitted to the agency in this NDA, and, most importantly, he's personally provided the detailed review and analysis of the safety data that you'll be hearing about today associated with the fomivirsen evaluation.

I'd like to turn the podium over to Dr. Chandler.

DR. CHANDLER: Thank you, Dr. Kisner. Good morning.

When I stepped down from full-time academic life three years ago, I sought to pursue two new things or different things for me in my professional life. The first was to take my long years in clinical trial work, my long years in basic and clinical research in ocular inflammation and infections, and apply it to drug development. The opportunity to work for ISIS Pharmaceuticals as a consultant was an ideal and has turned out to be a very challenging and wonderful experience.

Secondly, as many of you in this room know, when you get to be chairman, you get further away from patient care. And I wanted to go back to active patient care in a fairly sizable intensity, and I have been able to do that, including helping and being responsible for the ophthalmic problems of a cohort of approximately 200 people who are HIV-positive, many of whom have AIDS, working on a team with

two infectious disease subspecialists.

Today, I will share with you--may I have the next slide, please?--these trials and an integrated summary on efficacy. Then we'll turn to an integrated summary of safety, looking at all causality, all patients, all eyes. We'll look at a risk-to-benefit ratio assessment for fomivirsen, and finally, we'll in detail revisit the issues of the clinical data set size.

Next?

Throughout this, I will provide you information to let you make a decision that I believe will be yes: yes, fomivirsen is efficacious, yes, fomivirsen is safe, and, yes, the size of the data set is large enough to support the package label.

The patient size has already been mentioned: patients at the 165-microgram dose, 91, 118 eyes; at the 330-microgram dose, 239 patients, 315 eyes, for a total of 433 eyes that you will see.

Next, please?

DR. KILPATRICK: Dr. Chandler, may I interrupt you to ask which study or studies your slides refer to?

DR. CHANDLER: You will see individual numbers--I'm giving you the total size of the package that was investigated. I will provide for you at each study that we're talking about the numbers of patients.

DR. KILPATRICK: Forgive me for interrupting.

DR. CHANDLER: Thank you.

In terms of the exposure to fomivirsen, more than 150 eyes have had exposure to drug for more than 90 days. More than 85 eyes have exposure to drug for more than 180 days. The eyes that have been listed for you have had more than 3,590 intravitreal injections in total.

Next?

In terms of the assessment of CMV progression, standard criteria were used, two of the criteria being read on masked photographs by a fundus photo reading center, as well as being recorded at each clinical examination, the appearance of any new lesions of 750 microns in size and an advancement of 750-micron front of an existing lesion. In addition, two clinical criteria were also evaluated at each visit and were included in the analysis for progression: retinal detachment in an area of active CMV retinitis, and CMV retinitis that extended to adjacent to the optic nerve and was associated with a profound drop in visual acuity.

The efficacy endpoints were looked at in several analyses. Again, the primary analysis was the time to observed progression based on masked reading of the fundus photos for the first two criteria, and clinical evaluations for the third and fourth criteria. Secondary analyses that were conducted were time to observed progression with all

four criteria based on clinical examinations. Time to observed decreased border opacification as an indication of disease control was based on a clinical determination. In addition, time to treatment failure, which includes progression and patients who came off of study for ocular adverse events related to drug.

Next, please?

The photographs were read by Dr. Gary Holland and another colleague at Jules Stein Eye Institute. These were done in a masked fashion, and they were masked to one another. The slides that were reviewed were more than 19,000.

Dr. Holland needs no introduction to you. He has been an authority on CMV retinitis and other complications involving the eye and patients with AIDS for a long time. He has played an instrumental role in the evaluation of other drugs. He has written several papers in refereed journals detailing the criteria for judging time to progression and other facts that can be done and observed on fundus photographs.

Next slide.

I will show you today intention to treat analyses. In this, in the treatment groups, it includes any patient that was randomly assigned to the treatment who had a baseline day 1 visit with at least one intravitreal

injection and one follow-up exam. In the control groups, it was any patient that was randomly assigned to the control group who had a baseline day 1 visit and one follow-up examination.

In the safety data that we will look at, the data is generated from complete ophthalmic examinations that were conducted at each visit, routine laboratory tests that were done at baseline and at standard intervals throughout the time patients were on fomivirsen, and, finally, an intensive review of adverse event experiences reported by the clinical investigators.

First we're going to turn our attention to the question: Is fomivirsen efficacious? In this I'm going to share with you two trials and then some integrated efficacy data.

What you will see in the end from this section of the talk is that fomivirsen is effective for the local treatment of CMV retinitis in patients with AIDS. The treatment involves an inducting and a maintenance arm. The dose and regimen are based on prior treatment history of CMV retinitis. Patients with newly diagnosed disease are treated at the 165-microgram dose. The previously treating but uncontrolled patients had treatments with 330-microgram intravitreal injections.

CS2 shows efficacy in the newly diagnosed

patients. CS9 shows efficacy in previously treated patients that were uncontrolled on currently approved therapies.

First let's look at the immediate versus delayed study, CS2. Again, this involved newly diagnosed, previously untreated unilateral CMV retinitis that was peripheral. Zone 1 disease was not allowed. Again, treatment was at the 165-microgram dose. Randomization in this study was 2:1 between immediate treatment arm and delayed treatment arm. The primary efficacy endpoint, again, was time to observed CMV retinitis progression.

May we possibly move the microphone? We have a shadow.

Time to observed progression based on the masked reading of the fundus photograph, and then criteria 3 and 4, based on clinical investigation. Karnofsky scores for patients in this trial were 70 or better.

Here's the protocol scheme and design. Immediate treatment randomization patients had induction once weekly for three weeks injections of the 165-microgram dose of fomivirsen. In maintenance, they had injections every two weeks. The patients that were randomized to the delayed treatment arm were followed until clinical evidence of progression, and then were offered the opportunity to cross over into a treatment regimen that was identical to that in the immediate treatment arm.

Exclusion criteria typical: patients with external or intraocular infections. In this study, there was no allowance for systemic CMV therapy.

Next.

What you will see in terms of the data presented is an efficacy analysis that is based on a protocol-defined interim analysis, and that analysis will show you highly statistically significant results.

Here are the patient characteristics at baseline. The immediate group at baseline had 19 patients; the delayed had 10. There was a dropout of one patient in the immediate who did not meet the criteria for the intention to treat analysis, so what you will see is 18 patients on the other slides.

In terms of age and sex distributions, they are comparable between the two groups and typical for CMV retinitis patients with AIDS. Like you, I suspect, we were concerned about what might be the contribution to any treatment effect about CD4 counts or protease inhibitor use. The distribution between these two groups statistically is the same. I will show you analyses that deal with these covariates in a moment.

Here's the Kaplan-Meier plot on the intention to treat analysis for the delayed treatment group and the immediate treatment group, highly statistically significant.

Next slide.

Here you see the Kaplan-Meier data in the table form: 72 days for the immediate group to median time of progression, 13 for the delayed. The 95 percent confidence intervals do not overlap. The 25th percentile was 28 and 9 days, respectively, and note that one patient in the immediate treatment group is at 462 days at the time of the analysis that is still on treatment. The incidence of CMV progression was 44 percent in the immediate group and 70 percent in the delayed group.

In order to get a sense of how rapidly fomivirsen caused decrease in the border opacification, we used clinical determinations in the responders only. In other words, there were some people who did not show border changes.

In the 13 patients in the immediate group and in all 5 patients in the crossover from the delayed treatment group to the same protocol, the median time to decreased border opacification was 15 days. This indicates that within two doses, two individual injections, control of the infection was being noted in terms of decreased border opacification.

We also looked at the crossover group to look at what happened about their time to second observed CMV retinitis progression. There were five patients, again,

that crossed over to this protocol. The median time to progression was 99 days, and one patient at the time of analysis, and still ongoing, but at the time of analysis had treatment time with no progression of 673 days. This median time of progression also suggests that the patients that were in the delayed treatment arm were probably not different from those in the immediate treatment arm.

Next let's turn our attention to the potential impact of CD4 counts and protease inhibitors on patients enrolled in CS2.

Analyses were done to adjust for baseline protease inhibitor use. What they show is that baseline protease inhibitor use was not statistically predictive for time to progression. Further, time to observed CMV retinitis progression remains highly significant when adjusted for the presence of protease inhibitors.

The same analyses were done for adjusting for baseline CD4 counts. Baseline CD4 count was not significantly predictive for time to progression, and time to observed progression remains highly significant when adjusted for baseline CD4 counts.

Next?

Here is a scatter plot of CD4 counts at baseline for the immediate and delayed treatment group. Immediately you can notice that in this group there are two outliers,

but, otherwise, the cluster looks very similar for both the immediate and delayed group. I will show you a sensitivity analysis for the impact of these two patients in just a moment.

T1B We also had a subset of patients in which we were able to get CD4 counts over time, and as you can see, there are two that stand out here as having rather dramatic rises in their CD4 counts over the time that they were on the study.

Next, please?

The sensitivity analyses for these various individual eyes and patients show that exclusion from the statistical analysis of the two patients with the higher baseline CD4 counts--that's the first slide I showed you--confirm the treatment effect of fomivirsen, p = 0.0003. Exclusion from the statistical analysis of the two patients with highest CD4 counts over time also confirms the treatment effect, same p-value.

What can we say, then, about this trial. CS2, immediate versus delays. Fomivirsen is effective in delaying the progression of CMV retinitis in patients with newly diagnosed infection. Control of the disease is rapid, as indicated by the onset of decreased border opacification. And the treatment effect is significant with or without adjusting for the covariates of protease inhibitor use and

baseline CD4 counts.

We are aware that the advisory panel has received an alternative analysis of CS2. Once that has been presented, we would appreciate the opportunity to respond with other information that we may have.

Next slide.

CS9 is a schedule comparison involving--next slide, please?--previously treated, uncontrolled CMV retinitis. I will show you the range of things that these people and eyes had failed in a moment. The leading edge of the lesion could be on zone 1, as long as it was more than 1,000 microns from the fovea optic disc. Retinal involvement was more extensive. These patients had treatment with 330 microgram injections.

The randomization was 2:1 between a more intensive Regimen A and a Regimen B that was about half as intensive with the 330-microgram dose. The primary endpoint was time to observed progression based on the fundus photographs for the first two criteria and clinical investigation for Criteria 3 and 4. These patients has Karnofsky scores of 60 or better.

Here is the scheme for the protocol. Regimen A, the more intensive regimen, involved 330-microgram intravitreal injections on days 1, 7, and 15, three injections a week apart in the induction phase, and then in

the maintenance phase, an intravitreal injection every two weeks. Those who were randomized to the less intensive Regimen B had induction doses of the 330-microgram, again, same concentration, days 1 and 15, and then maintenance intravitreal injections every 4 weeks.

The exclusion criteria in CS9 were similar to CS2 with the exception that Ganciclovir implants had been in place for less than 6 months. Those eyes were excluded. And if patients required extraocular CMV therapy other than oral Ganciclovir, they were excluded. In other words, oral Ganciclovir use was allowed in CS9.

Between the two groups, Regimen A and Regimen B, the distribution of the various baseline characteristics is comparable. The age-sex distribution, again, is typical for patients with AIDS and CMV retinitis. Retinal involvement was more extensive but comparable in the two groups.

Next, please.

CD4 counts between the groups, again, were comparable. Protease inhibitor use was comparable. Oral Ganciclovir use between the two regimens was comparable. We will analyze for all these covariates and show you those analyses in just a moment.

Next?

As I mentioned, to be enrolled in CS9, these were patients who were previously treated but uncontrolled on

approved available therapies. There were a total in the two regimens of 54 patients. Virtually all of them had been treated once, and usually several times, with IV Ganciclovir, oral Ganciclovir in 39 percent, Foscarnet intravenously 52 percent, and it includes 13 percent of eyes having been treated with Cidofovir.

Next?

Here is the Kaplan-Meier plot for Regimen A versus Regimen B. As you can see, Regimen B, the less intensive regimen, has a long shoulder, then a sudden drop just above the median time to progression. I will show you analyses to take that into account in a moment. The p-value shows that these two treatment regimens are not statistically significantly different.

Next?

Here's the Kaplan-Meier plot analysis in a table form. Median days to progression straight off, 106 for Regimen A; 267. The confidence intervals overlap. Maximum days to censor are similar in the two groups.

To take in account that long shoulder, interpolated medians were calculated. We believe that the more true indication of where this median time progression for these two regimens resides is at 90 days. The 25th percentile, 42 days. The incidence of CMV retinitis progression, 47 for Regimen A, 30 for Regimen B.

Next?

To put in context that 90 days median to progression time, just put in the efficacy for systemic DNA polymerase inhibitors in newly diagnosed disease. These are approved. They go from 30 to as much as 120 days. We believe that the 90 days median time progression in patients who have failed these therapies is very impressive.

Next?

Again, to get an indication of how rapidly the disease, the infection would be brought under control, time to observed decrease border opacification was evaluated. The median time progression to decreased border opacification in each group was 8 days, with similar minimums and maximums, indicating that after a single 330-microgram injection in eyes that were failing all other approved therapies, control was achieved.

Let's look now at the impact of various covariates. Since these two regimens had similar median times to progression, in looking at the CD4 count data, we have chosen to pool the patients and show it in aggregate. We have looked at patients whose CD4 count at baseline or any time of the trial was higher than 50 versus those who were 50 or less. Those that were greater than 50 never reached a median time to progression. Those that were less than 50 had a median time to progression that was at 73

days. Let's show this in table form in the next slide.

Seventy-three days for patients with less--50 or less CD4 cells who had failed all the other approved therapies and were moved to this trial. For those with higher than 50 cells, the median time to progression was not determinable, but certainly it is likely to be higher than the 113 days as the lower limit of the 95 percent confidence interval.

In terms, then, of the prognostic value of the baseline characteristics, CD4 counts of 50 or greater are a positive prognostic factor for time to progression in CS9. Baseline characteristics that were not predictive for time to progression included baseline protease inhibitor use, the extent of the retinal involvement, or oral Ganciclovir use.

Overall, the efficacy conclusions from CS9 are as follows: Fomivirsen provides durable control of CMV retinitis in patients with previously treated, uncontrolled retinitis. Fomivirsen provides rapid onset of decreased border opacification after a single dose, indicating that the disease is starting to be brought under control very rapidly. There is no significant difference between the two regimens with regard to time to progression; that is, the more intensive regimen was no better statistically than the less intensive regimen. But, again, to emphasize also, the durable control of 73 days in patients failing other

therapies was achieved even when the CD4 counts were 50 or less.

Here is just to put together for you some integrated efficacy analyses. Look first at the previously untreated 165-microgram. When all the eyes are included that are available, the median time is 70 days. It was 71 in CS2. Then look over here in the previously treated patients with Regimen B, the less intensive regimen, and Regimen A, a total of more than 100 patients, the median time to progression is in excess of 100 days.

So let's return to the first question. Is fomivirsen efficacious? Yes, the 165-microgram fomivirsen does demonstrate statistically significant efficacy in the treatment of newly diagnosed CMV retinitis. And, yes, 330-microgram intravitreal injections of fomivirsen given according to either the intensive Regimen A or the less intensive Regimen B is efficacious in the treatment of CMV retinitis that was unresponsive to currently approved anti-CMV retinitis therapies.

I'm going to talk for a few minutes on the pharmacokinetics of fomivirsen. This is sort of to give you a sense, one, why the efficacy is there; and, two, will lead into some of the comments I will make regarding safety.

In preclinical studies--and here we see one example, in rabbits--the vitreal disappearance of drug has

been calculated, and the uptake by retina of drug is in the square boxes that you see here. What you see is over approximately a 10-day period, disappearance of the drug from vitreous, but a longer concomitant uptake and hold of the drug in the retina.

Next, please.

CS5 is the human study that we are doing in patients who are scheduled for Ganciclovir implants who are enrolled and given a single intravitreal injection of either 165 micrograms or 330 micrograms of fomivirsen; and then at the time of surgery, with a specific interval, a small amount of vitreous is obtained to study for measure of drug concentration at the same time plasma is obtained.

Here you see the curve for the vitreal disappearance of the 165-microgram dose over approximately the same time points as you saw in the preclinical studies. While we can't obtain whole retinas from these patients, it is seemingly reasonable to assume that the curve for the retinal uptake and disappearance would be similar to that I just showed you.

In terms of the plasma pharmacokinetics, no detectable concentrations of fomivirsen or its metabolites were detected in any of the plasma samples taken from patients who either received the 165- or the 330-microgram injection.

Next?

In conclusion, then, fomivirsen is a local treatment. The clearance of the drug from vitreous is similar to that we showed in the animal studies. Fomivirsen given by intravitreal injection is not detectable in plasma. Following a single injection into the vitreous, concentrations in the vitreous at days 1, 8, and 12 remain above the in-vitro EC50 for the virus. Patient enrollment continues in the studies in CS5.

Next let's turn to the issue of is fomivirsen safe. What I will be showing you is integrated safety data for all causality, whether investigators thought it should be attributed to drug or not.

Again fomivirsen in these integrated safety data include the eyes at 165, 118; 330, 315 eyes at that level, a total of 433 eyes. There will be one exception to this that you'll see toward the end, and that is, when we looked at confidence intervals, we took all the data but counted eyes only once. There were some patients who were allowed to cross over from one protocol to another over the years of the studies. Those eyes have only been counted once in terms of integrating all the data and looking at it once.

Again, safety assessments are based on the complete ophthalmic exams, the routine laboratory tests that were obtained at baseline and at stated intervals, while

patients were on treatment, and a review then of the ocular events--recording of ocular adverse event experiences noted by our clinical investigators.

What you will see through this is that fomivirsen is safe for the local treatment of CMV retinitis. The incidence of ocular adverse events is low both in previously untreated and previously treated eyes, treated at the 165- or 330-microgram dose levels, respectively. Most of the adverse events resolve while the patients continue on treatment. Few severe ocular adverse events were reported and required removal from study. And, as I will show you in detail, the retinal detachment rate, despite all these repeated intravitreal injections, is low.

In terms of systemic safety, no deaths were attributable to fomivirsen. No systemic adverse events were considered by investigators as probably or possibly related to the drug. In terms of laboratory abnormalities--and there were lots of laboratory abnormalities in these patients because of their underlying disease and their other treatments. But there was no pattern that was attributable to fomivirsen.

In terms of characteristics of the ocular adverse events--and here is where we focus our attention--the overall incidence is acceptable. Most of the ocular adverse events were mild to moderate in intensity, as judged by the

treating physicians. And the resolution rate for the more common adverse events was itself very common.

Let me set you up with these slides so that it will be easy for you to follow through. You're going to see a series of slides where COSTART term is on your left, patients eyes that were treated at 165 micrograms are here, 330 less intensive Regimen B here, and the most intensive regimen will be on your far right.

Anterior chamber inflammation is the COSTART term that we used for patients with anterior uveitis. Uveitis is a COSTART term that we used when the investigators described or labeled it as posterior uveitis. I left the term vitritis since several clinicians used that term, and we had vitreous haze as one of the things that was graded in our forms. I believe you can put these together and say this is the posterior uveitis.

In terms of anterior chamber inflammation, 6 percent of our patients entered the study with evidence of anterior uveitis, and approximately 30 percent of the patients previously treated and uncontrolled entered these trials with pre-existing baseline inflammation. These are the ocular adverse events that were recorded. The incidence of anterior uveitis, 11 percent at 165, 10 percent at the less intensive Regimen B, 20 percent at the more intensive Regimen A.

If you put these together, 7 percent, 20 percent, and 20 percent for posterior uveitis. Our other most common reported ocular adverse event was that of increased intraocular pressure. These tended to occur within the first few injections of fomivirsen. Intraocular pressure levels were not an eligibility criteria for entering it. We had several patients whose eyes had pressures greater than 24 at baseline. We even had two eyes enter that were hypotonous with pressures of zero.

There was within that a fair amount, 12 percent, 12 percent, and 20 percent, of increased intraocular pressure reports, usually for one or two visits, and either spontaneously resolved or treatable with topical beta blockers. There were a few eyes that had anterior chamber paracentesis for acute rises in pressure, and it was managed without any problem. But, again, I want to underscore that this is increased intraocular pressure that tended to be transient, and I will show you the resolution rate in a moment.

Cataract, this COSTART term, for the most part in our studies indicates lens opacities. Only six eyes in the entire fomivirsen package had cataract surgery.

Next, please?

In terms of the severity of these ocular adverse events, same set for the moment, there were a few eyes that

were judged as having severe intensities of these various COSTART term ocular adverse events, but by and large they were mild to moderate in intensity.

Next, please.

In terms of resolution, increased intraocular pressure, 82 percent of the 165 and, when you put the 330s together, 94 percent resolved. It was not a lasting problem. Similarly, if you looked at anterior uveitis, posterior uveitis, most of it resolved during the time and patients could continue on study. Some of our investigators found--we talked about this at an early investigator meeting, and they started treating patients preemptively with two or three, four times a day of 1 percent penicillin acetate, or its equivalent, and found that they could easily manage these patients without having inflammation be a problem that needed--caused withdrawal.

The other thing I want to assure you is that we aren't talking about a big fibrinoid uveitis with these. There was only one patient who had uveitis/vitritis to the extent that it required a vitrectomy. There were two eyes in our entire trial who had clinical diagnosis of endophthalmitis, both presumed to be microbial, one proven. So there were three eyes with really, really intensive posterior uveitis, and I have detailed those for you.

Next, please.

Other changes that were recorded of interest to you: For our trial, cystoid macular edema is angiographically proven cystoid macular edema. Retinal edema includes those for which there was a clinical diagnosis or some other description of retinal edema. So you can see, again, there is something of a trend toward these being more common as you get to the more intensive higher-dose level. But, again, keep in mind that those are the eyes that have failed other therapies as well.

RPE stippling. A lot of you have heard about the issue--and it's been talked about in the press and everywhere else--about RPE stippling being a problem with fomivirsen treatment, and it was seen early in our trials. The overall incidence, 3 percent in 165, none at the less intensive regimen 330, 4 percent at 330-microgram doses. This was looked at very carefully by our clinicians. It was also scored in all the fundus photo reading center reports at every visit. It turned out not to be a problem.

Retinal disorders are primarily epiretinal membranes and other descriptions of things that we are seeing in the literature more and more commonly described for patients with CMV retinitis.

Vitreous hemorrhage, the incidence was low. This was not, except for one case, a real big problem. So with all those 3,590 intravitreal injections, very low incidence

of vitreous hemorrhage.

Here is, again, the scoring by severity for this same group. Again, by and large, the majority of them are mild to moderate in intensity.

Next?

Three other COSTART terms that I thought would be of interest to you: desaturation of color vision, 1 percent in the 165, none, 4 percent. Again, a story that many of us heard very early in studies, in trials with fomivirsen, was peripheral vision decrease. It turned out overall not to be a problem: 3 percent at 165, 4 percent at the more intensive Regimen A.

At the time when we noted this to be of concern, we instituted protocol revisions and started having visual fields done using automated visual fields for a possible. This was a challenge in patients with multiple problems, but of those that we could evaluate, 2 percent at Regimen B, 2 percent at Regimen A have documented peripheral field changes using a 3060-2 type of format, or its equivalent. It was not a big problem.

Next, please.

In terms of severity, again, notice this preponderance, even of these uncommonly reported things, of them being mild to moderate in intensity.

Next?

Retinal detachment rate. For the previously untreated eyes treated at the 165-microgram dose, the incidence was 3 percent. For the eyes that were previously treated and uncontrolled with other approved therapies, and then treated in the 330-microgram intravitreal injection protocols, the overall incidence was 9 percent.

What about eyes that had to be discontinued because of ocular adverse events? All of the data I've given you so far is all causality. Here is all causality for eyes that came off at 165, 8 percent, 12 percent, 18 percent. With the exception of the 165 group, almost all these were felt to be in some way related to the drug. Again, notice there is something of a trend here toward Regimen B 330 being more like the treatment group with 165 in terms of the incidence and severity in certain ways of these ocular adverse events.

Overall, what can we say about the safety profile? There were no reported systemic adverse events attributable to fomivirsen. There is an acceptable safety profile regarding ocular adverse events. The retinal detachment rate is low. There is a low rate of discontinuation of eyes from studies due to ocular adverse events. The ocular adverse events were predominantly, in terms of intensity, mild to moderate. And for the more common ones I showed you, a very high resolution rate of those, of ocular

inflammation and ocular increases in pressures. Overall, the trend in the safety profile favors Regimen B over Regimen A.

Just to comment again, to pick up the points I made along the way, retinal pigment epithelium stippling was uncommon. Peripheral vision decrease was uncommon. And documented visual field defects were rare.

In terms of management, I've already told you some of these points, but I will review them. Increases in intraocular pressure were transient and were highly manageable, usually with topical beta blockers. Intraocular inflammation was effectively controlled with topical steroids, either to be used in response to inflammation or, as I said, some investigators started using topical corticosteroids preemptively. Some investigators found in some of our trials that they could omit a dose of fomivirsen when inflammation seemed to be difficult to control and see a reduction in intensity that allowed them then to continue dosing thereafter.

The safety profile is favorable for fomivirsen, and it supports the label of newly diagnosed being treated with 165 micrograms in the regimen we've described, and the previously treated, uncontrolled on currently available and approved therapies being managed with the 330-microgram dose. And based on the equal efficacy and the trend toward

a better profile in terms of safety for Regimen B, we believe that it should be Regimen B, that is, an induction every other week for two doses, followed by, every fourth week, maintenance injections.

Next, please?

Let's turn to the third question. Does the clinical experience with fomivirsen justify approval? We'll go through several other points other than those that we have made before.

Overall exposure we'll talk about again. I'll show you a visual acuity profile. In the end, what is more important, as we heard earlier from one speaker, than having your visual acuity preserved? We'll look at the upper limit of the 95 percent confidence intervals for these various adverse events to give you assurance based on a worst-case scenario of what those adverse event incidences might be. We'll look at the probability, given our data set, of detecting rare events--that is, could we have missed, how likely was it that we missed an important ocular adverse event? Then I'll make a couple of comments about the incidence of contralateral and systemic CMV infections in the experience with fomivirsen.

In terms of days on fomivirsen, the mean, again, you receive the same format: 165, the less intensive Regimen B 330, more intensive A. The means were all in

excess of 100 days. The medians were in excess of 50 days. Importantly, maximums, 813 days, 463, 972. Some patients have had long, long experiences with many, many injections.

Next?

Again, to go back, on the basis of the 3,590 individual injections, the exposure of eyes at 165 and at 330 includes 150 eyes with more than 90 days' exposure to drug, 85 eyes with more than 180 days' exposure to drug, and a fairly extensive experience of eyes with 9 months' and longer; and as you saw in the preceding slide, some for two, going on three years.

Let me set these up for you to talk about the retention of visual acuity across treatment. Eyes that are 20/40 or better at baseline are down here. Worse than 20/400 are at the top. Across here are the last visual acuity measures. The first slide you are seeing here is 165-microgram dose patients, 20/40 or better here, worse than 20/400 there. White boxes are eyes that had the same visual acuity at entry and at last measure. Those that are yellow are better. Those that are blue have had a decrease, which is not surprising that we would have some, given the natural history of CMV retinitis.

Of the eyes that entered the study with 20/100 or better vision, this group, 84 percent at their last measure had visual acuity in that range. Those at the last measure

that had visual acuity of 20/40 or better were 66 percent.

Next, please?

Here's for Regimen B 330 micrograms, the same exact layout. Here are the patients' eyes that have the same visual acuity at baseline and at their last exam; better above in yellow; those that have decreased below in blue; those that entered and left the study with 20/100 or better, 80 percent; 56 percent at the end of the study had visual acuity of 20/40 or better.

Next, please.

Next we'll talk about the worst-case scenario based on the upper limit of the 95 percent confidence intervals.

You'll see the same COSTART terms, plus I put a few others in for you that I thought would be of interest, all causality. Again, here the n is 405, that is, an eye, no matter how many protocols it was treated in, and any cross-overs or rollovers, was only counted once. And this lumps together those that were treated at 165 and those that are treated at 330.

The overall incidence of anterior uveitis observed was 17 percent. Again, I want to remind you that coming into the study, 6 percent of those at 165 and an average of 30 percent of those at the 330 came in with some baseline inflammation.

In terms of posterior uveitis, here's your overall incidence of 15 percent. Upper confidence interval for those two combined is in the range of 20 percent.

Hypotony was not an issue with this drug. The observed incidence was 1 percent. Upper confidence limit would be 3 percent. The commonly observed increased intraocular pressure--and, again, 80 to 94 percent between the two groups of those resolved--16 percent. Upper confidence limit would be 19 percent.

Glaucoma, with glaucoma's field changes and optic nerve changes, was distinctly rare in our study. Cataract, I mentioned to you, really means lens opacities with the exception of the six patients who had cataract surgery, 8 percent, upper confidence level 11.

Next, please.

I'm just going to show you again the same groups. Cystoid macular edema, retinal edema, retinal disorder--primarily of the retinal membranes; retinal artery occlusion was rare; the RPE stippling.

I mentioned the endophthalmitis. Again, to underscore, we had two patients with clinical diagnoses of microbial endophthalmitis, one of which was proven microbiologically. Overall retinal detachment rate of 8 percent; worst-case scenario would be 11 percent for the entire group.

Then, again, these three COSTART terms, 4 percent, 3 percent, 1 percent; then 6, 5, and 3. These are not issues in this drug.

Let's turn it the other way and ask the question: If the true incidence of a rare adverse event is 2 percent, given our n of 405 eyes, the probability is 99.4 percent that at least one rare adverse event would have been observed. If the true incidence is 1 percent, that probability is 93.6 percent that at least one rare ocular adverse event would have been observed. We do not believe that there is an under-reporting of rare ocular adverse events based on this size of data set.

A couple of comments about extraocular CMV. It was reported in 3 percent of our patients, with an upper confidence level of 4. We are not in any way making a claim that intravitreal injections of fomivirsen have anything to do with the control of extraocular CMV. This rate is probably an under-reporting, but it is what is in our data set.

In terms of contralateral eye disease, of the 276 eyes that entered the study with unilateral disease, 9 percent developed contralateral disease. Again, I want to put some caveats on that. Except for CS2, we allowed oral Ganciclovir use. If you take our purest study in terms of saying what is the incidence of contralateral disease, it

would be CS2 where we had four cases, for an incidence of approximately 20 percent.

Next, please.

So based on these safety issues, yes, the clinical data set size is adequate. We have more than 150 eyes treated for at least 90 days, and most of them far beyond that. The upper limit of the 95 percent confidence intervals indicate an acceptable safety profile. There was a high rate of resolution of the most commonly reported adverse events. Although I haven't shown you the data, there is no evidence of cumulative toxicity. The clinical data set is sufficient to assess the safety of fomivirsen.

In terms of efficacy, we believe strongly, with the data that we have, with the analysis which supports the statement, yes, the 165-microgram intravitreal dosing in CS2 demonstrates highly statistically significant efficacy for the treatment of newly diagnosed CMV retinitis. The p-value indicates something of a one in ten thousand likelihood that that is due to chance alone.

Let's step back for a moment. I have given you very rapidly an enormous amount of data and data analyses, and I can assure you it is but the tip of the iceberg of what is in the database.

What do we know? CMV causes progressive irreversible retinal destruction. In untreated cases, the

probability of retinal detachment to over a year is 50 to 60 percent. We know from the SOCA trials that visual acuity does decrease in the range of a loss of one line every 2 months to one line every 7 months. And, yes, unfortunately, there is also some decrease in peripheral vision as measured by visual field scores.

We hope it doesn't, but we think that there is a reasonable possibility of the reemergence of CMV retinitis, currently, with an armamentarium of drugs all with the same mechanism of action and the likelihood of cross-resistance somewhat already proven.

In that context, think about fomivirsen. Fomivirsen is effective in the treatment of CMV retinitis: newly diagnosed at a dose of 165 micrograms in the regimen I showed you; previously treated, uncontrolled disease at a dose of 330 micrograms in that less intensive Regimen B.

Fomivirsen has an acceptable safety profile. There are no systemic adverse events. The ocular adverse events are mild to moderate in intensity, and the common ones tend to resolve. Visual acuity is highly retained in patients treated with fomivirsen. The retinal detachment rate is low. The data set size is adequate to substantiate the package label.

Again, here is what the package label looks like for newly diagnosed and previously diagnosed infections. I

won't repeat it at the moment but simply ask for the last slide.

Finally, for me, a couple of personal comments. When I was a junior faculty member at the University of Washington, I was also the first ophthalmology consultant at the then-new Fred Hutchinson Cancer Research Center, and I saw my first cases of CMV retinitis in severely immunosuppressed patients without anything to treat them with.

In the early 1980s, I, like some of you, saw the early cases of CMV retinitis in patients with this newly diagnosed condition of AIDS--again, with no therapies.

Happily, through research, good clinical trials, and commitments, we have some treatments. Unfortunately, what I see is the treatments are all similar in terms of their mechanism of action.

While we are enjoying a period of reprieve thanks to, again, great research in the control of HIV, we are facing the issue of patients who are resistant to those drugs, can't take them or are intolerant, currently don't have options. And if there's anything I've learned from working with AIDS patients, they're well informed. They know, and they want to have the best. They want to have the best for them in terms of safety, the best in terms of efficacy, and the best in terms of not unduly impinging on

their quality of life and their style of life.

We believe firmly--I believe firmly based on my work with fomivirsen that this is a drug that has an important place in the management of CMV retinitis.

Dr. Kisner, I'd ask you to come back to the podium for any concluding comments.

DR. KISNER: Actually, I don't have any concluding comments. We'd like to do the best we can now to answer any questions the panel might have regarding what they've heard and what they've received from us or the agency.

CHAIRMAN WILSON: We will open the floor then for questions. Dr. Kilpatrick, did you have a question that you wanted to ask?

DR. KILPATRICK: I'd like to direct my question to Dr. Chandler.

DR. CHANDLER: Surely.

DR. KILPATRICK: Dr. Chandler, with regard to the 405 eyes--

CHAIRMAN WILSON: There's a mike right there, Jack, whichever you like.

DR. CHANDLER: With regard to?

DR. KILPATRICK: With regard to the 405 eyes--and I'm being a devil's advocate here--if you added up all of those adverse events, you get nearly 100 percent. So I'm asking: What percentage of eyes had no adverse effects?

DR. CHANDLER: Implied in your question is two things: what percentage of eyes had none and what percentage of eyes had multiple.

Approximately 30 percent, 35 percent of the eyes accounted for about two-thirds of adverse events reported. For example, the patient I mentioned with microbiologically proven endophthalmitis accounted for five severe ocular adverse event reports. Then there were roughly 25 percent of the patients that had no adverse events reported.

DR. KILPATRICK: A follow-up on that. Of the 30 percent who had some, one or more adverse events, what's the upper limit on that?

DR. CHANDLER: The highest number?

DR. KILPATRICK: No, not the highest number of events, but the upper confidence limit. Of 405--

DR. CHANDLER: I haven't calculated it.

DR. KILPATRICK: Okay, but that could be high. It's going--it's obviously more than 30 percent.

DR. CHANDLER: Yes.

DR. KISNER: I can amplify just a little bit. Actually, the number of patients that had no adverse events whatsoever is 30 percent. Jack said 25. I think actually the number is 30. And of the patients that had severe adverse--patients with adverse events, only about 20 percent of the patients had adverse events that would be categorized

as serious according to the mild-moderate-serious grading.

CHAIRMAN WILSON: Any other questions from the panel? Don?

DR. FONG: I had a couple questions. Dr. Chandler presented the numbers in the CS2 group as 18 in immediate and 10 in the delayed group, and I was just looking over Table 19 in the booklet that was printed out, and I see that there's 26 patients in the treated group. What is the difference in number there?

DR. KISNER: I'm going to have to get an answer to that. There are patients that are in that list potentially who were delayed therapy patients who experienced the progression and were crossed over and then actively treated. I believe that's the answer to the question.

DR. FONG: I see. I also had one other question. HAART therapy was initiated sometime--widespread use was initiated during the course of the treatment. Did you guys look at sort of the use of HAART throughout the trial as maybe like a time-dependent covariate or something?

DR. CHANDLER: Keep in mind that our study truly spans pre-HAART, initiation of HAART and the era of patients controlled. And in this, what our database allowed us to do was to look at potentially the role of HAART therapy in terms of adverse events.

What I can tell you is it's not clean. I believe

that there is no significant impact that we can truly speak to at this time of HAART therapy. I showed you the data on CD4 counts, protease inhibitor use, such as we have it, as something of a surrogate to try and address that question.

What I had thought might happen in terms of cumulative event rates was that, as patients were on study a long time, we would start to see an upswing of things like reports of adverse events of inflammation, as an example, or anything else.

Cumulative over time, as indicated by numbers of doses, does not upswing on patients who transition from pre-HAART into the post-HAART therapy time. So I don't have any evidence to suggest, one, that the drug is more difficult to use in terms of adverse events with patients on HAART therapy, nor do I think that HAART therapy per se contributed to the events that I have described.

DR. FONG: So you do know who has been on HAART, so you could do a time-dependent analysis if you wanted--

DR. CHANDLER: The problems that we have is we have data like that, but most of this is data based on the patient's recollection of dates. And you would see things that I'm pretty sure didn't happen, like people being on double HAART therapy at once and so forth. And there was enough confusion about dates that I'm very reluctant to state to you a definitive statement on that issue alone.

Keep in mind that these people average nine or ten medications and they often don't have, at least in our experience, clear indications of when they started and stopped various medications. And so I'm very--I want to be very conservative about making any claim one way or another.

DR. FONG: It seems like, you know, if you're doing a clinical trial, you would be able to monitor any or all additional therapies that are given to the patient enrolled in the protocol.

DR. CHANDLER: Our investigators worked in concert with infectious disease subspecialists, and, clearly, the needs of the patient overall were of primary, paramount importance and took precedence over doing what you and I would love to do, a very clean trial, maintaining very strict eligibility criteria about this treatment or that treatment.

We wanted our patients to have the best possible management of their HIV disease as judged at whatever stage they were, whatever stage they were in the history of HAART or pre-HAART by their treating internist, infectious disease subspecialist, and the like. We did not interfere with that in any way.

CHAIRMAN WILSON: Ms. Cohen?

MS. COHEN: Yes, I have a series of questions. Going to your Slide 18, you talked about 433 eyes treated.

Well, is that single eye or is it double eye? Is it the same person? How many people does it represent? And does each eye respond differently than the other? I'm not getting a feeling--I'm getting a feeling of eyes, but I'm not getting a feeling of people, and I'm not getting a feeling of how they respond clinically.

DR. KISNER: The number is 430 eyes. That has--it corresponds to 230 patients. To answer an important, very important question that you asked, that is, we do not see necessarily similar responses between eyes when a patient has bilateral disease and they're treated, either with regards to efficacy or with regards to safety.

We looked very carefully at this issue as we were analyzing the data, and it became very clear to us that both for efficacy and for safety, the observational unit of interest because the eye as opposed to the patient. Clearly, we looked at patients, we've done all of our analyses by patients as well. But, very clearly, in a patient who has bilateral disease, neither the safety or the efficacy in response to fomivirsen are all that similar, and we felt it was critical to look at the safety database and the efficacy with regards to eyes.

It is a local therapy, so we want to be sure that you understand that.

MS. COHEN: Go ahead, Jim.

DR. KILPATRICK: Dr. Wilson, I'd just like to follow up on that. May I suggest that if you do go forward to do further randomized studies, that you consider, if that's the case, randomizing eyes rather than patients? It would make a much cleaner clinical trial.

DR. KISNER: Certainly, that's something that should be considered.

MS. COHEN: Now, how important is the injection technique? And can anybody do it? And is there leakage of the vitreous fluid in the process? Can I go to anybody and they're capable of injecting it? Or you have to find out what their techniques are, how good they are?

DR. KISNER: Clearly not. This does require specific training. I'd like to have Dr. Chandler, who's more qualified than I am, talk about the procedure and actually address that question. But, clearly, it requires training to do this.

DR. CHANDLER: The injection itself we believe will be practiced by the people in ophthalmology who are most accustomed to doing this already, and they are people who are vitri-retinal specialists and people who specialize in the management of ocular infectious and inflammatory diseases, uveitis and so forth. These are the people who most often are having referred patients with intraocular infections of other types or intraocular inflammations,

where they do these injections on a fairly frequent--fairly frequently.

I believe that most ophthalmologists are very capable of doing the injection, but I don't think that a lot of them will be comfortable because they aren't doing it on a relatively frequent basis. So my suspicion is that it will be the group I have outlined for you.

MS. COHEN: You know, that worries me. I'm looking at your Slide 32. You talk about males and females, but you don't talk about cultural differences. And AIDS and HIV aren't in big cities alone. A lot of people don't have access to major clinical centers, and they're going to have to depend upon what's available in the community. And who are these people who are going to be doing it? I'm concerned--you know, I don't know what your make-up is, but as a consumer member, I'm always concerned that we think about, you know, major clinical centers. But that isn't the way the world is, and that isn't the way the United States is.

DR. CHANDLER: I fully agree with you. I am now one of those people. With my step-down from full-time academic life, I live in a community of 100,000 people 90 miles away from Seattle.

MS. COHEN: That sounds good to me, as a matter of fact.

[Laughter.]

DR. CHANDLER: It's wonderful.

I represent the care in that community, and without that care, people were faced with going 90 miles.

I have looked in detail--my wife happens to be the head of one of the regions for the management of AIDS and distribution of monies for regimen treatment in the State of Washington. And we've looked at this together very carefully. And at least in the State of Washington, with where we know the patients are, we have qualified people, at least in our part of the world, in all of those areas. No patient would have to go more than an hour in the State of Washington to have someone very highly qualified do it, and I think that's true of almost everywhere. You go to a relatively unpopulated state, there's still these infections. A lot of them occur in agricultural--not AIDS patients now with CMV retinitis, but other things that require intravitreal injections, and there are people who have mastered it. They may not have subspecialty training in the two areas I've told you about, but they have been sort of the one that has been the community expert, if you will, in handling these patients.

MS. COHEN: My question about vitreal--the leakage of vitreal fluids from injections, that wasn't answered, and also the cultural diversity make-up of the patients.

DR. CHANDLER: Okay. Let me answer the leakage. That is very rare. These injections are done with a 30-gauge needle, so thin that you--it's very thin. You don't make a big tract with this, and there is virtually no leakage of any fluid as you remove the needle through the sclera.

MS. COHEN: I--excuse me.

DR. CHANDLER: And we can give you some more demographics if you would like that now, or--

MS. COHEN: Well, we can do it later. I'm interested also--I noticed in your document until the lights went out last night--we lost our power here. I noticed that there was a difference between the injections of humans and animals, and there was a difference between animals I noticed between the rabbits and the mice. So how does this then extrapolate to humans?

DR. CHANDLER: If I understand--and I believe I do--the essence of your question, in terms of injections and what was seen in terms of the response of tissues--is that--

MS. COHEN: Yes.

DR. CHANDLER: There is very clearly a species difference among various species of animals on how they respond in terms of inflammation after the injection of an oligonucleotide, including this one. And we believe that that's probably comforting because of two facts: one, it

overestimated but gave us ahead reason to be looking for these in humans; and, two, it gave us an opportunity to look at the possibility that the use of topical corticosteroids, or in some of the animals we did periocular injections just to have a stabilized dose, showed amelioration of those.

Further, they also gave us strong evidence that any changes we saw in the retina were in almost every case related to inflammation and not to a direct toxic effect, cytotoxic effect of the drug. So they really gave us a fair amount of assurance.

MS. COHEN: I just have a couple small ones. I just wondered how the visual acuity was measured. I heard that--you know, there's acuity and there's acuity, so I don't know what that means.

DR. CHANDLER: These were standard Snollen(?) visual acuities. These were not done with--or we did not have DRS-style things for all these.

MS. COHEN: Okay. And just one other brief question. I was curious at this gentleman over here who spoke in talking about his results. Is the treatment with other medications--I didn't know. I thought you said you weren't taking any antivirals, but I wasn't sure. But how is this in relationship to people being treated with other medications? And how do you know which is which and which does what?

DR. CHANDLER: Well, again, in CS2, in terms of managing the CMV retinitis, the only drug was the fomivirsen. With regard to treatment of the CMV disease in the other trials, oral Ganciclovir was allowed. In all of our analyses, we had the group set up so that we could compare those two and very clearly determine a drug effect that could be related to the fomivirsen.

With regard to--I believe the other part of your question is, quotes-unquotes, immune reconstitution with a highly effective antiretroviral therapy role, the data so far do not support that that is the issue.

Now, you might ask some of our long-term patients, have we taken them off treatment or recommended, we have left that decision to the treating clinical investigator. And in most cases, they have decided that these patients, these eyes, were best managed by keeping them on therapy.

MS. COHEN: The cultural difference one, also, I'm curious to know and I would like to know the make-up, your male and females and with different backgrounds that they come from, because there could be some different response to the medication.

DR. KISNER: Let me see the demographic slide.

MS. COHEN: Okay. I don't think--did we see that? I'm sorry if we did.

DR. KISNER: You have not seen this.

MS. COHEN: Okay. I thought, well, maybe I did, maybe--

DR. KISNER: This is the demographic make-up for the entire population of patients contained in the analysis. You can see that the gender balance is 91 percent male, 9 percent female. And the racial balance is listed as you see there, 68 percent Caucasian, 11 percent black, both North American, African Americans, and blacks from South America, because these studies were also performed in Central and South America. Asians were 4 percent, and the other category includes Hispanics as well as both North and South American Native Americans.

The demographics, of course, for CMV retinitis population reflect the demographics for the acquisition of HIV disease that precedes it by maybe 10 years. And these studies were performed from the beginning of--end of 1993 through the beginning of this year, and it's actually our view that these demographics are probably not so different than the demographics of HIV acquisition in the late 1980s, although we do think that there's probably some areas that are somewhat underrepresented.

MS. COHEN: Thank you very much.

CHAIRMAN WILSON: I think this is an appropriate time to take a break. There will be opportunity to ask some more questions later. There's one question which I'm just

going to ask now, and you can formulate your thinking about this. But I'm going to want to explore the question of how many patients this therapy is likely to benefit. Given the small numbers in your study and the difficulty in recruiting at the latter stages of your study, the implication is that there is going to be--there is increased resistance to current therapies and a resurgence of the CMV retinitis. But I haven't seen any data to that effect, and if anybody has any, that would be some information that I think would be useful to us as we evaluate this.

So if you can just give that some thought, and maybe after the break and after the FDA presentation, you'll have an opportunity to address that.

So, 15 minutes, 10 minutes after 10 o'clock.

[Recess.]

CHAIRMAN WILSON: Dr. Chambers will now give the FDA presentation.

DR. CHAMBERS: Thank you very much. I am going to go through a quick summary of my review of the clinical data and some of the other issues. The information that I am going to go through was all contained in the draft medical officer's review, which the committee has all received.

Next slide, please.

The stated proposed indication you have seen before. It is formally written as Vitravene would be

indicated for the local treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome.

Next slide, please.

Just as a reminder to everybody, there are a number of chemistry manufacturing control issues. There are some pharmacology toxicology issues, which we are not addressing at this meeting. In the event that the committee recommends that the product be approved and the agency concurs, that does not necessarily mean the product will be available tomorrow. There are other issues that will need to be resolved, and the agency is committed to continue to work with the sponsor to go and resolve those issues. But I just wanted everybody to be aware this is not--the clinical issues are not the only issues that are involved, not just with this product but with any product.

Next slide, please.

There are a number of studies that were conducted. They are listed as CS1, 2, 3, 5, 7, 9, and 12. I've actually never asked why there was skipping of the numbers, but it was never a particular issue. But these are the studies that were presented to me or as part of the application.

Next slide, please.

CS1 was the initial pilot study. It was an open

label study which contained 22 patients. It was a dose-ranging study, and the only major conclusion that you can draw from that is the 83 dose was not effective. It did lead to the suggestion that additional trials should be conducted, and consequently, they were.

Next slide, please.

Just as I quickly go through them, I'm going to go through the studies that I am dismissing relatively quickly, not because they are any less significant but just because we have less information on them or have gained--are able to gain less information.

CS5 is the PK study. At the time of the NDA submission, there were 10 of 28 patients enrolled in that study. Our conclusion based on that was that there were not sufficient number of patients because of--in order to draw conclusions. We hope that that study both continues and that we are able to get the full results of that study in the near future. But there are several arms that were not fully enrolled in order to be able to get information from that study.

Next slide, please.

CS7 was an open label extension for patients previously enrolled in other trials. At the time of the submission, there were 118 patients. Again, it does not have a control group by design. These patients were all

enrolled in one of the other trials, and it was designed to capture longer-term safety information. And to the extent that it does that, it is helpful, but you have to bear in mind there is no control group in order to be able to establish baseline safety and efficacy information. So you can derive only limited safety information because of the lack of control.

Next slide, please.

CS2 you have heard some about. It was an open label, dose comparison trial. The original planned enrollment was 60 patients, and at the time of the NDA submission, there were 45 enrolled. This has been a recurring problem with a number of the studies in that there were planned-for numbers that we thought were adequate to be able to evaluate the objectives, but the sponsor--and you've heard some of the reasons, but there are a variety of reasons that they were unable to enroll the number of patients that were projected.

Next slide, please.

You've heard something about the numbers of the individual slides. There were photographs taken of each of the patients that we tried to evaluate efficacy on. I have personally reviewed all of those slides. This is not unusual for this application. It's the same thing that was done for the Ganciclovir application, Foscarnet application,

Cidofovir, Ganciclovir implant. This is the standard routine that the agency has used to evaluate any of the CMV retinitis products.

Patients that I was able to evaluate in CS2, there were 16 patients in the 150 immediate group, 8 patients in the 330 immediate treatment group. There was a dose escalation started at 150. There were three patients there, dose escalation starting at 75. There were 4 patients there, and there was a deferred group where there were 8 patients. Again, this is not necessarily the number that started. This is the number that I was able to evaluate based purely on looking at slides.

Next?

The graph here shows the Kaplan-Meier curve based on my reading of the particular slides. There are a number of differences, and I will talk a little bit later on about why some of the calls are different, not for you to make a determination of which call you think is better or worse, but there are some real clinical judgment differences about why calls were made one way or the other. And it's my opinion that those are based on clinical judgment and there is not a right or wrong answer to those particular calls. But because the number of patients is so small, it only takes a couple patients called slightly differently, and in some cases, a weak different--or in some cases calling

something a progression at one point in time or not calling it then and then having the disease go away or people being censored can have a tremendous impact.

My conclusion from this particular trial was that there was some efficacy being demonstrated in the 330 dose, and in the 150 dose I could not--there were not enough patients and there was too much variability for me to be able to tell what was going on. Even in the 330 dose, it's relatively small, and the line goes straight across because there were no progressions in that time in the 330 dose. But the time that's being evaluated is all short. You see this graph only goes to 112 days, and you see the blue line even stop before it even gets there. That's because everybody got censored before they ever got there. The same thing with some of my other lines. They don't go even the full length of time out.

Next slide, please.

MR. FROST: Dr. Chambers, could I ask a question before you go forward?

DR. CHAMBERS: Absolutely.

MR. FROST: Does that Kaplan-Meier curve correspond to the one that's in your review?

DR. CHAMBERS: It is very close. The draft review is a draft review. There was subsequent to that a discussion between the sponsor and myself over a number of

patients, and I re-examined a number of different patients that were there, including two patients who had--were crossed over, and consequently, I had--they had been treated as no progression, and I carried the dates farther, not knowing if they had actually then become on treatment. And they actually should have been censored at the point that treatment got started.

MR. FROST: I see.

DR. CHAMBERS: There was another patient that was inadvertently left off the earlier graph.

MR. FROST: Were you masked to the treatment assignments at the time that you did the fundus photography review?

DR. CHAMBERS: Yes. At the time that I looked at the fundus photographs, I had eight boxes of fundus photograph slides. I had no--I did know the patient number. I knew the study that they were in. I had no clue about whether they had started treatment, ended treatment. That was the first thing that I did with this review before I had looked at anything else.

MR. FROST: So these graphs are actually driven by a masked review of the photographs.

DR. CHAMBERS: That's correct.

MR. FROST: Okay.

DR. CHAMBERS: That's true of both mine and the

sponsor's. Dr. Holland's group and such were also blinded. Dr. Holland's group, it's my understanding, is still blinded to the information. I am obviously no longer blinded, but was at the time that the slides were reviewed.

Next slide, please.

CS3 is another one of the trials. It was originally set up to be a much more definitive answer because it was comparison to oral Ganciclovir, and it had some initial arms into it and some difficulties with the 330 dose and, consequently did not get carried out the way it was originally intended. The planned enrollment was 174 patients. The planned interim analysis was at 90 patients. That trial has not gotten up to even the planned interim analysis point because there were only 49 patients enrolled.

Next slide, please.

Again, as far as evaluable eyes, 150 immediate group, there were 29 for me; the 330 immediate group, there were six. Dose escalation 150, six patients, dose escalation 75 group, four patients, and the Ganciclovir group, eight patients. Again, this is not the way the study was originally designed, but because of a variety of circumstances, it's the results that I had to work with.

Next slide, please.

This is the Kaplan-Meier curves. This should be the same as what was in the review. Again, you see a

relatively short line. It is the blue line. Although it does not show any progressions to the 330 dose, the time before people got censored is very short. The Ganciclovir group also shows relatively high amounts, but this is small numbers of patients. And that's the biggest message that I have in both of these two studies, is that it's not possible to differentiate in many cases the different groups here because of the small number of patients and the errors that would be associated with the potential curves; and the possibility of just reclassifying one or two patients can change these curves fairly dramatically.

Next slide, please.

CS9 you've heard discussion about. It was a comparison between Regimen A and Regimen B, Regimen A being weekly treatments for three weeks and then fortnightly evaluations, Regimen B being every two weeks or fortnightly evaluations times two, and then monthly exams.

Next slide, please.

CS9 was planned to have 100 patients. There was a planned interim analysis at 40 patients. Enrolled at the time of the NDA submission were 54. The number of evaluable eyes for my review was 39, which included 29 in the weekly group and--starting out weekly group, and 10 in the group that started fortnightly.

Next slide, please.

The curve here may be a little misleading because it's a three-dimensional curve, but these curves are not statistically different. And you cannot make a determination that there's any difference between these groups as far as efficacy of these two. There actually is a cross point along there. It just looked a little bit prettier if I did it three-dimensionally. Two-dimensional is in the review.

Next slide, please.

Adverse events, though--and I have selected a number of adverse events that I thought were particularly important to focus on. There is a difference between the weekly and fortnightly, and you will see the weekly doses having significantly higher percentages as far as numerical percentages. In many cases, again, they are not necessarily statistically significant because of the low numbers. But there is a clear trend that there are higher percentages in the weekly group than the fortnightly group.

Next slide, please.

Actually, let me back up one. Sorry.

While I have assigned percentages along here, I cannot emphasize enough that these are based on small numbers and these percentages vary tremendously with a single patient changing. So I wouldn't--I do not view these percentages as being hard and fast numbers.

Next slide, please.

CS12 was designed in the same way as CS9 was but, as mentioned, was conducted with European investigators. Again, Regimens A and B are the same.

Next slide, please.

I'm skipping most of the details because you've heard most of these before. Planned enrollment was 120 patients. The planned interim was 40 patients. And this trial is only at 32 patients at the time of NDA submission. Of those, there were 27 evaluable eyes, 14 in the weekly group and 13 in the fortnightly group.

Next slide, please.

Again, you see curves that run very similar to one another. They are not statistically distinguishable.

Next slide, please.

Again, adverse reactions, where you see more adverse reactions in the weekly group than the fortnightly groups. Again, I would not focus on the individual numbers because they are based on small numbers of patients. But there is clearly a trend to having more adverse reactions in the weekly group than the fortnightly group.

Next slide, please.

I think because you're hearing different stories it's worth going through a little bit about why there are some differences in the time to progression. As I mentioned

earlier, I do not believe that there is a necessarily right or wrong answer to when retinitis progression occurs. For an individual patient, it's an evaluation made by the treating ophthalmologist as they are looking at the slides over the course of time. In the case of photographs, people reviewing the photographs are forced to look at what they have in front of them. That means in some cases the views that are taken are of what would be considered the relevant area by the person looking at the slides. In some cases, they have sufficient overlap to be able to tell where you are within the eye. And in some cases, the areas where you would like to see just don't exist.

There are some clinical judgments that will account for some of the differences, and I want to reiterate that slight differences in decisions can lead to fairly large differences in the recorded time just by either censoring or not censoring patients.

It's particularly true of cases where there may be slight disease progression over the first couple weeks and then resolution of the disease. So that if at week one, two, or three, one reviewer calls it progression and the other reviewer does not think the disease has advanced enough to be considered progression, they would censor that patient at the time of the last observation. In other words, neither--one person may say that it's a progression

at week two, and if the other reviewer does not believe there's progression at week two, while both reviewers say the disease then proceeds on and resolves, the way we score these, one would say there's a progression at week two and the other one say that it's censoring at, say, week 150. Those are very big differences for what may be a relatively small call at week two. It may have progressed 100 microns as opposed to 150 microns. So relatively small differences maybe in a single photograph may lead to relatively large changes.

I'm not sure that I'm particularly happy with that system that developed as far as scoring the things, but it is the scoring system that we've used for each of the CMV retinitis products in the past, and we did it again for this product to maintain consistency. I'm also not sure that I have a better way to score them, or I would have probably suggested that a while ago.

Next slide, please.

There are some differences in discussions with Dr. Holland--between Dr. Holland and myself that may also lead to some differences. I tended to require more complete baseline than Dr. Holland may have necessarily done. If I was unable to evaluate two or more visits in a row, being able to see whether the slides either were too light, too dark, or non-existent, I tended to censor people at that

particular time because I could not tell what was going on during that period of time, and I did not want a long gap where I could not tell what was going on.

Dr. Holland in some cases--and I'll let him correct me if I misquote him--was able to in some cases later on determine that there was no scarring in a particular area, and although he did not necessarily have photographs earlier on, because he did not see any scarring or any evidence of retinitis in that location later on, say that retinitis had not occurred in that location.

I was unwilling to make that call. If I could not actually see retinal photographs at the particular time points, I censored patients at that time.

The same thing with baseline views. If I could not get an adequate--if there was not an adequate view in my mind of different areas of the retina to be able to tell where retinitis was occurring, I censored those patients.

The third issue--and I may talk about, try and demonstrate some of it with some photographs momentarily--has to do with where the location of the border is when you have satellite lesions. Borders of CMV retinitis are not always clear-cut. In some cases they are; there's a very clear border. In other cases, there are a few satellite lesions. And most people reviewing CMV retinitis slides agree that just filling in areas where there are significant

satellite lesions already is not really progression. There were a couple satellite lesions, and that's where the border probably should have been. Where you call the border when there are a couple of satellite lesions is a clinical judgment call and may vary between reviewers.

T2B Next slide, please. Slides on, please. Thank you. And can we get the lights down a little bit more, please?

I'm not sure how well this is going to view, and, again, the purpose of these is not to ask people to make a call about which was the right decision on things, but to give you an idea of why some of the calls can be a little questionable or may vary.

The border at the top--the top area has CMV retinitis or is assumed to have CMV retinitis, and you don't see a straight border. You see areas of hemorrhage. You see right before the vessels there a couple small areas of lightening which are presumed to be or may potentially be satellite lesions. So the border here is not necessarily clear.

This particular slide was--you might not be able to see it--was done one week after the slide you just saw, and I apologize for not having dual projection so you could go and compare them directly. But you'll notice some areas--flip back. This is the first slide. And this is the

second slide.

You'll notice two things. One, the orientation...you'll notice where some of these vessels are, if I flip--sorry. You'll notice the orientation is different. This is the same. Magnification is different. The orientation is different. So that it makes it sometimes difficult to be able to look at some of the areas you wanted to look at where you thought there might be progression. But this is that same area, and the inclusion in along here may in some cases be called progression. But because there were some satellite lesions that are along here, some people may not call it progression.

Again, two weeks later, it has advanced farther, but there is some hemorrhage here and there is some question along these lesions. Again, some of these calls can be questionable.

Moving on to a different patient, this is the baseline that was seen, and again you see an area and some satellite--potentially satellite lesions. You see this particular vessel to give you some orientation. You again see that vessel. You now see some streaks where some other vessels were, some potential vasculitis. You see a slide that is very light and difficult to evaluate. But this is that next particular week or the next visit in two weeks.

If we go back, the location of the vessel has

changed a little bit. The picture is a little bit fuzzy because of some of the haze that's involved.

This a different vessel that was located back down over here on an earlier photograph, so the orientation, again, is different.

This is that same vessel along here. Now you can see the area of the border.

Again, magnification now changes. You can see the border a little bit better, and in some cases progression might be called here.

A different patient. You notice the haze that's here? This photograph is not out of focus as far as projecting it. It's what was presented. Making calls about there is CMV retinitis that's down along here, making calls about really where the border is along here, is a difficult call.

This photograph does not have that same border area. It has the vessel that's up along here, and I'll go back. I mean, you can see some of the vessels through some of the haze. You can see how much clearer they are when the haze goes, but the orientation is slightly different.

Again, back, the same kind of the vessel and some of the haze. You see some of the retinitis. A spot along here, that vessel.

Just because some of the vessels get partially

obliterated and some vasculitis is going on does not necessarily mean that the retinitis has progressed all the way up to that point. You'll see the vessel go back to being intact later on.

You'll see it here looking much better.

This is one last area.

Again, these are theoretically the same location.

Again, I'm showing you just so you can see what kind of differences in some of the orientation.

Can I have the proxma(?) back on? And next slide, please.

My conclusions from the review were that there appear to be some efficacy. I clearly saw cases where CMV retinitis that I would have expected to progress was stopped. But the number of patients is small, precluding an accurate estimate for me of what that--the day or days before progression, that number that you heard mentioned by the sponsor as being 70, 100, whatever. I'm not confident enough in what I was able to evaluate to say that I know what that number definitely is.

Most of the studies that were submitted were submitted prior to the scheduled completion. That was problematic.

Next slide, please.

I do believe you can say that the fortnightly

injections appeared safer than and no less effective than the weekly injections from studies 9 and 12. The mechanism and potential visual effect of some of the retinal pigment changes I do not believe has been fully characterized. You have heard a little bit about them. The incidence is relatively low. But I'm not sure exactly what they are. They clearly did occur in a number of patients, both early on and were observed later on. I'm not entirely sure what they are due to and how much significance to necessarily attribute to them.

Next slide, please.

As far as mean visual acuity changes, again, I did not feel there were enough patients to be able to clearly determine how much change in visual acuity was necessarily preserved in patients. Visual acuity is not a prime endpoint that we've used because it is tied primarily to the location of CMV retinitis, and if you don't have CMV retinitis affecting the central fovea area, you will not necessarily affect large sections of visual acuity. But it was one of the analyses that we looked at, and I was unable to determine whether there was a significant impact on visual acuity. And I mentioned earlier that there were chemistry deficiencies that will need to be corrected.

Next slide, please.

From the start, I believe the pharmacokinetic

study CS5 needs to be completed as originally designed so that we can get some of the pharmacokinetic information. Additionally, because these trials did not go to their completion and do not have what I view as an adequate safety database to completely characterize the product, I believe that additional clinical studies should be done. Whether they need to be done Phase 3 prior to approval or whether they need to be done Phase 4, I have not reached that conclusion, and I am looking for input from the committee.

Next slide, please.

Based on my review and the small number of patients, I do not believe there's adequate information to support a first-line therapy. But first-line therapies are not the only potential therapies that can receive approval. Consequently, I believe that consideration needs to be given for an indication in which people have failed previous therapies. Those patients were clearly studied in this application. There are clearly patients that benefited in that particular case.

I have not entirely ruled out a first-line indication, but I think it's very unlikely based on the current data set that we have.

Next slide.

Thank you, and I'll take any questions.

CHAIRMAN WILSON: Dr. Kilpatrick?

DR. KILPATRICK: Dr. Chambers, thank you. I just have a number of small questions.

First of all, what does the FDA and the sponsor mean by open label?

DR. CHAMBERS: Open label means that neither investigators nor patients were blinded and to what therapy group they were in.

DR. KILPATRICK: What do you mean by an evaluable eye? And let me go on, if you like. What is the difference between your definition of an evaluable eye and the sponsor's? In total, how did this affect the numbers that the sponsor presented and those that you are considering today?

DR. CHAMBERS: When I looked at the photographs, there would be a packet of photo--a number of photographs labeled with a particular patient name and the dates that they were observed at. If I only had a baseline photograph for a particular patient and had no subsequent follow-up visits, I did not consider that patient to be evaluable because I could only see that they had retinitis at the beginning.

If I could not determine at baseline where retinitis was, I did not consider them evaluable. If I had no photographs on the patient, I did not consider them evaluable.

If there was an insufficient area, I could not see where the borders were of the retinitis for subsequent photographs. I did not consider them evaluable. If the photographs were too dark or too light to make that call, I did not consider them evaluable at the start.

Subsequently, if there were long periods of time where I could not evaluate, I might censor the patient at that particular time. But those patients were still evaluable. Evaluability had to do with what I saw at baseline or the first visit.

DR. KILPATRICK: And the number 405 sticks in my mind from Dr. Chandler's presentation, but you were really looking at a very much small number of photographs. Isn't that correct?

DR. CHAMBERS: That's correct.

DR. KILPATRICK: In terms of eyes.

DR. CHAMBERS: I looked at all the photographs, to my knowledge, that were taken and that had been submitted with the NDA at the point that the NDA safety database was cut off. All of my efficacy evaluations were all done based on what I had in hand as far as photographs.

DR. KILPATRICK: Thank you.

DR. FONG: Just a quick follow-up to his question. Was there a different--

CHAIRMAN WILSON: Dr. Mathews?

DR. MATHEWS: Dr. Chambers, do you have some information on some of the definitions of the covariates? The protease inhibitor variable in CS2, was protease inhibitor used at baseline, not including any subsequent protease use?

DR. CHAMBERS: I did not extensively look at the--submitted as part of the application are the use of other medications along there. The numbers were too small, as far as I was concerned, to make any kind of distinctions in subgroups of whether people were on protease inhibitors or not. The time when CS2 was run, there was relatively little use of protease inhibitors. That's not true of trials 9 and 12 where there was much more extensive use of protease inhibitors.

DR. MATHEWS: But, still, you know, I agree the sample size is very small, but CS2 is their pivotal efficacy trial, and there were substantial differences in the prevalence of protease use, I assume at baseline--is that correct?--not at entry into the trial, and also in CD4 counts, and we haven't heard anything about HIV viral load. And I'm not convinced, after looking at the sponsor's presentation, that something hasn't been missed in terms of an alternative explanation for part of the treatment effect.

In other words, how many of the patients who never respond--who failed to progress would be classified as

responders to antiretroviral therapy with low viral loads, independent of what happened in the CD4 count? Because it's--you presented--the sponsor presented CD4 data, but it's well-known that somewhere around 20 to 30 percent of patients have discordant responses between CD4 and viral load, and they still have clinical benefit.

So, you know, with the small sample size I think the covariate adjustment issues are very critical to making a judgment whether efficacy has been demonstrated.

DR. CHAMBERS: I don't disagree with you that it can make a difference. What I'm commenting on is the estimate that you would put as far as a covariate analysis when the numbers are--when you're talking about two or three patients, the assumption within the models of which way that goes are not particularly good because you only have two or three patients to base that on. And I don't know how to interpret those differences.

To the extent that there are differences between groups, I agree, that's problematic. I just don't know how to correct for it because of the small numbers. But I don't think the standard statistical approach to correcting for it--it just leaves you with very wide estimates and doesn't give you a definitive answer.

CHAIRMAN WILSON: Dr. Fong?

DR. FONG: Yes, just to follow up on Dr.

Kilpatrick's question, I wanted to find out, was there a differential in the number of ungradable eyes between the treatment groups?

DR. CHAMBERS: I do not believe that there was. I did not formally count up--well, no, I did formally count up those. I did not see a differential between--unevaluable eyes tended to be based on photography, not based on clinical characteristics of the patient or follow-up evaluations.

DR. FONG: Also, you were talking about having two evaluators of the fundus photograph, and you were talking about differences in interpretation. Did you guys adjudicate? Did you talk with each other to decide what might be, you know, an acceptable interpretation of the photographs between the two of you?

DR. CHAMBERS: There were discussions regarding CS2 as far as where we differed and some discussion about how some of those calls were made. Following that discussion, I went back and re-reviewed each of the patients that we had had a discrepancy on. It's my understanding that Dr. Holland also went back and looked at either all or most of the patients that we had discrepancies on. We have agreed to disagree on the particular call that's been made.

I understand why--I can speak for myself. I understand why the call was made by Dr. Holland and the

manner that he made them, each of the particular cases. I just differ in opinion either where the border actually is or what is satellite filling in or whether--as I said, some of them are differences in I did not count people--I treated them unevaluable if I couldn't see a particular area. Dr. Holland was willing to, if later on he saw that particular area and did not believe there was any lesions that he could determine were scars, say that there was no retinitis there. I was unwilling to do that.

CHAIRMAN WILSON: Mr. Frost?

MR. FROST: Well, just a quick comment and then a couple of questions. One, I just want to respectfully disagree with Dr. Mathews regarding viral load in that I don't think--while I understand the importance of viral load in assessing disease, I don't think there's any data to suggest that HIV viral load independently impacts upon CMV or the progression of the disease. In fact, I would argue just the opposite based on Mark Jacobson's data from UC-San Francisco that suggests, despite low viral load and immune reconstitution in the face of HAART, patients are developing CMV disease, which might suggest that, in fact, the pathological process for CMV is quite independent of HIV viral load.

So I'm not sure that based on a lack of knowledge of HIV viral load within the context of these clinical

trials we can't still independently measure some sense of the efficacy of fomivirsen in these studies, especially when one accounts for the fact that randomization may well take care of any issues that are implied in your suggestion of viral load, although the numbers, as Dr. Chambers clearly points out, are very small. And I think it's dangerous to try to make those scientific leaps without real clear data to support those positions.

Dr. Chambers, a couple of questions. Throughout your reviews and the studies that I looked at in terms of the Kaplan-Meier's, you didn't make estimates in terms of time to progression in terms of days. You were uncomfortable with that?

DR. CHAMBERS: I did not have the statistical package in my computer at the time to do the errors around them, and so I thought it was misleading to report the days without reporting what the error bars are around them. I have asked one of our FDA statisticians to--they have taken my raw data and will ultimately generate that. But that has not happened yet.

MR. FROST: With that in mind, then, in several of your comments that follow each of the studies, you referred to--and in your concluding remarks, you referred to evidence of efficacy. So if I were to press you, in your judgment, based on what you've seen, does fomivirsen sodium show

evidence of efficacy against CMV?

DR. CHAMBERS: I believe there are patients that--I believe I saw slides of CMV retinitis that behaved differently than it would in its natural course in that it stopped progressing faster in some patients than I would have expected it to progress. The disease is relatively characteristic in a number of cases, and while it can be slowed down because of other things that happen with the patient, the findings that I saw are more consistent with a drug effect acting on those particular patients.

I have the--in subsequently looking through, I have the impression that it's the 330 dose that was capable of doing that, and while the lower dose, the 165, did appear to slow it down, it did not do it fast enough, in my mind, to be clear that there was clear efficacy at the 165 dose.

MR. FROST: You didn't say a whole lot about the safety package, and I think there's probably some general sense that the safety package is small. But essentially the same question, based on the safety package that you reviewed and the adverse events that you saw, in your opinion is fomivirsen sodium safe? Can it be safely administered in patients who have CMV retinitis?

DR. CHAMBERS: The adverse events that I have seen are not unusual for events of this type of--for this type of product. The database I view is too small to be able

necessarily to detect some of those cases. While you've heard the number 405 or 410 or in the 400s as far as eyes treated, two-thirds of those people did not even go--or two-thirds of those eyes did not even go past three months. I viewed that being a sufficiently small database that there could be events that we have not seen. And I am, as I mentioned earlier, unclear about what to make of some of the retinal pigment epithelial changes.

MR. FROST: Does that safety database differ dramatically from the other products that have been approved in the sense that rather than overall number of patients, which might be useful, obviously, if there were more, but rather in terms of time of exposure? I remember sitting on this committee for the Cidofovir hearing, and the overall time of exposure to Cidofovir was really quite short.

So I am wondering if we're not in a relatively similar circumstance in that it's quite possible that there might be events that have been missed because of the relative limited number of patients, but does that differ dramatically in terms of time of overall exposure to the product itself?

DR. CHAMBERS: The database in front of us is smaller than what was seen for Ganciclovir IV, Foscarnet IV, dramatically different than Ganciclovir implant. It is not--it is small than the Cidofovir database, but not by much.

I would suggest, though, that we may have missed a number of events with Cidofovir which we are now detecting, which I'm sure you are familiar with.

MR. FROST: I would probably concur with that opinion. Just one last question, Mr. Chairman.

Your concluding remarks make a differentiation between first-line therapy and second-line therapy. There are five, now, approved medications for CMV retinitis if one includes oral and IV Ganciclovir separately. Have we ever made that distinguishing--have we ever distinguished between first-line--I know the answer. I know you know the answer. We've never made that distinction prior, have we?

DR. CHAMBERS: We have not made that distinction for CMV retinitis products. We have made it very frequently for a number of other products in the systemic area and a number of other ophthalmic products.

MR. FROST: I think that's true, but certainly in the area of HIV we've made that distinction in antiretrovirals. Is it your opinion that that distinction is useful in terms of how the product will actually be used?

DR. CHAMBERS: As you can probably guess, I do not know, since we haven't done it before.

CHAIRMAN WILSON: Dr. Kilpatrick?

DR. KILPATRICK: Dr. Chambers, I'd like to come back and tell you what I'm hearing you say, and I'm asking

whether this is accurate or not. I want to bring you back to your statement about this unknown statistical package with errors, which presumably mean standard errors.

DR. CHAMBERS: That's correct.

DR. KILPATRICK: But as I take it, the thrust of your remarks is that these sampling errors, confidence intervals, are--the confidence intervals are themselves very wide, as we've seen from the sponsor's presentation. The sources of non-sampling error may, in fact, be much wider and that we have to take into consideration from all of your considerations from the different evaluation examiners and the potentials for bias.

DR. CHAMBERS: I think I'm relatively consistent, as I go through and read the things, and I have gone back and read things again multiple times and have generally agreed with what I put down, based on the way I read things. I am not beginning to say that the way I read things is the way everybody in the universe necessarily reads them. So I think there is variability that is legitimate variability between readers. This is not the first time that I've read a particular group of slides and Dr. Holland has read a particular group of slides and that we've had disagreements. They are not uniform in one direction or the other. In some cases, I made calls earlier, in some he makes calls earlier, in both this and other data sets. So I think there is some